Magnetic Resonance Imaging in Clinical Therapeutic Trials of Multiple Sclerosis

THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE includes a review of magnetic resonance imaging (MRI) of multiple sclerosis lesions by Jack H. Simon, MD.[1] This article is particularly timely because currently there are more clinical therapeutic trials in multiple sclerosis recently completed, under way, or planned than ever before, essentially all of which have incorporated or will incorporate MRI. The reason for its inclusion in these trials is MRI's extraordinary sensitivity for identifying the pathology of multiple sclerosis and its safety on repeated use. For reasons that are not fully understood, however, the relevance of the MRI picture to the clinical status of individual multiple sclerosis patients has been less than optimal.

Multiple sclerosis is a difficult disease for which to establish meaningful clinical outcome measures because its natural history is one of unpredictable relapses and remissions of neurologic symptoms and signs. The patients' clinical condition usually improves spontaneously, at least temporarily, making identification of a therapeutic effect difficult. Despite the clinical fluctuations, the usual course of multiple sclerosis is one of successively less recovery from relapses and the slow development of increasingly severe residual physical disability, which is usually permanent. Previous therapeutic trials have convincingly shown that certain regimens could prophylactically decrease the severity and frequency of relapses but not alter the accumulation of physical disability over time, which is the most important factor affecting the lives of multiple sclerosis patients. The value of MRI, or any other measurement, as a clinical surrogate in multiple sclerosis must be the closeness of its match to physical disability.

As Simon points out, several studies conducted to date revealed that the correlation between the currently used MRI measures and physical disability in multiple sclerosis patients was only modest.[1] The reasons for the less-than-optimal correlation are unknown, but may relate to the fact that the most common MRI appearance of a multiple sclerosis lesion—increased signal intensities on T2-weighted images—is nonspecific and does not distinguish minimal (for example, increased water space) from severe tissue destruction (demyelination plus axonal loss). Furthermore, although gadolinium enhancement on T1-weighted images is produced by pathologically active lesions—blood-brain barrier disruption, inflammation, edema—such MRI active lesions are identified four to ten times more frequently than are clinical relapses by history and physical examination. This discrepancy may result from the fact that only a fraction of the active lesions may occur in anatomically sensitive areas of the central nervous system—optic nerves, brain stem, spinal cord—the majority occurring in areas that are relatively "silent" in terms of producing clinical symptoms and signs. Extreme examples of the MRI-clinical features mismatch include the autopsy discovery of classic multiple sclerosis lesions in the brains of patients who died of nonneurologic causes and who had been neurologically normal their entire lives.[2] Undoubtedly, most of those lesions would have been identified by MRI had it been performed during life, but these findings would have had no relevance to their clinical states. Still, there are cases in which the correlation seems particularly good. Filippi and co-workers showed that certain quantitative changes in lesions observed on serial MRIs in patients at risk because of isolated monosymptomatic syndromes could identify those in whom multiple sclerosis developed after five years.[3]

It is impossible to predict at the beginning what a given patient's course will be over the next two to five years, and, like patients with certain other relapsing diseases, those with multiple sclerosis may experience rather profound placebo effects during the course of a therapeutic trial, which must be taken into consideration. These effects have included a reduction in the clinical relapse rate by 25%[4] and changes in peripheral blood natural killer enhancement and suppression, indicating a systemic immune response.[5] Thus, whenever ethically possible, therapeutic trials in multiple sclerosis should include a randomized placebo arm to distinguish therapeutic from placebo responses. Moreover, in the recently published interferon beta-1a (Avonex, Biogen) study, which showed a substantial clinical lessening of physical disability and a benefit on the relapse rate in the interferon beta-1a–treated group, there were decreases in both T1-enhancing and T2-hyperintense lesions in the placebo-treated group as well as in those treated with the active drug (albeit not to the same extent).[6] This observation underscores the importance of a placebo-treated control group in studies assessing the efficacy of treatments on MRI-identified multiple sclerosis lesions. Whenever possible, we must be able to identify and quantitate the reduction in the lesions resulting from placebo treatment before attributing decreases observed to a given active drug therapy.

Simon clearly summarizes the natural history of multiple sclerosis lesions detected by MRI from acute through chronic stages. Obviously, an important use for MRI in future multiple sclerosis therapeutic trials will be the documentation of pathologic changes serially over time, realizing that there may be considerable discrepancy between a patient's MRI and clinical profile. Other readily identifiable uses include screening for entrance into therapeutic trials—that is, identifiable active lesions present or absent; preliminary assessment of the efficacy of a putative therapeutic agent for decreasing active lesions, which could substantially reduce the time required in phase I and II evaluations; and the use of new variables such as T1-hypointense lesion volume on standard MRI and decreases in *N*-acetyl aspartate levels on proton magnetic resonance spectroscopy, both of which may prove to be stronger surrogates of physical disability than the standard MRI measures of multiple sclerosis that are used at present.

At this time, MRI might be used as a primary outcome measure in certain small phase I and II trials for the initial assessment of therapies on active lesions. Full-fledged, pivotal phase III trials, however, must have a clinical out-

come—of which physical disability is most important—as the primary measure of efficacy, with MRI relegated to a secondary outcome status.

LAWRENCE JACOBS, MD
Department of Neurology
University of Buffalo School of Medicine and Biomedical Sciences
Buffalo, New York

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Hepatitis C Virus—A Pathogen for All People

HEPATITIS C VIRUS (HCV) is a positive-strand RNA virus that infects 3.5 million people in the United States and that is acquired in large part by parenteral or sexual modes of transmission.[1,2] The prevalence of HCV differs depending on the patient group under study. In patients with previous injection-drug use, the prevalence is as high as 90%; in patients with a history of posttransfusion hepatitis not due to hepatitis B, the prevalence is about 85%. Even in patients at low risk for parenterally acquired infection, healthy blood donors who have been prescreened by sophisticated questionnaires for risk factors associated with the transmission of infectious agents, the prevalence of HCV infection is about 1%. Thus, HCV is a virus that infects people in all walks of life and in all sections of society and as such represents an enormous public health problem. Three key questions must be addressed to aid clinicians in the care of these patients:

- What is the natural history of those with infection?
- Given the likely variability in natural history between patients, who are those at risk for progressive disease?
- Is effective therapy available?

The article by Tong and co-workers in the May 1996 issue of THE WESTERN JOURNAL OF MEDICINE examines the first two questions.[3] The answer to the last question is under intensive investigation, and all three questions have been incompletely resolved.

The natural history of HCV infection remains the subject of great debate. Whereas the virus persists in most of those who acquire infection, progression to clinically important liver disease occurs in some but probably the minority of those who are infected. The controversy lies in defining the proportion in whom disease develops and in determining the time over which progression to complications occurs. Discrepancies in results from different studies are likely due to differences in study design. Studies of natural history have differed in the manner in which patients have been selected (population-based studies versus referral-based studies) and the risk factor for infection (blood transfusion versus injection-drug use). In one study of patients with HCV infection and a history of previous blood transfusion who were referred to a tertiary referral center, 15% died of complications of liver disease or hepatocellular carcinoma over a four-year period.[4] Moreover, 51% of patients had cirrhosis at the initial presentation, and hepatocellular carcinoma had already developed in 5%. This study portrays HCV infection as a serious and rapidly fatal disease.

The current study of Tong and associates in the May issue of the *Journal* also included only patients referred to a liver clinic, but it examined the natural history of HCV in a somewhat younger group (mean age at presentation, 44 years) with a different risk factor for acquiring infection (injection-drug use).[4] Both of these differences are of possible relevance because the acquisition of virus by injection-drug use may carry a better short-term prognosis than the acquisition of virus by transfusion.[5,6] A person's age when the virus is acquired is also likely to be relevant because the time interval between exposure and the development of complications is probably long—20 to 30 years.[7]

Hence, if the virus is acquired early in life—for example, through a brief period of injection-drug use in the late teens or early 20s—infection would be predicted to play an important role in overall life expectancy in the ensuing decades. In contrast, if the virus is acquired later in life, comorbid conditions rather than HCV infection will likely determine life expectancy.

Tong and colleagues found in a large study group (125 patients with a history of previous injection-drug use) that at presentation, 36% had histologic evidence of cirrhosis and 0.8% had hepatocellular carcinoma. As with their study of patients with HCV infection following transfusions, the time interval between the presumed exposure (the onset of injection-drug use) and the detection of cirrhosis or hepatocellular carcinoma was long—19 and 26 years, respectively.

The rate of death was lower in the second study than in the first, however—2.4% within two years versus 15% within four years, respectively.[4] These findings support but do not prove that acquiring the virus by injection-drug use carries a better short-term prognosis than acquiring it by transfusion. The authors also attempted to examine the additive effect of alcohol use on HCV-related liver injury. One would predict that the duration of infection associated with severe disease would be shorter in those with a history of heavy alcohol use than in those without, but such an effect was not found. The confounding effect of alcohol on the natural history of HCV infection remains to be clarified.

At first glance, HCV would appear to be an aggressive pathogen in which serious liver disease occurs in the majority and progressive disease can occur over a rela-